

# DiNEH Project Update: Survey → Clinic → Mechanisms



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# With acknowledgement and thanks to the Team!

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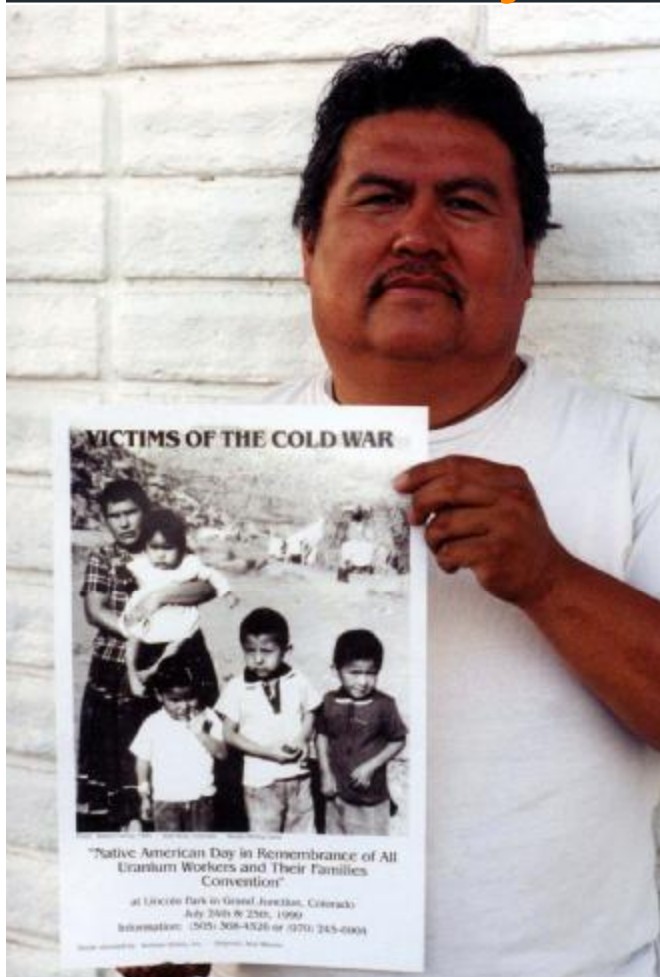
Navajo Nation Office  
of Vice-President,  
HEHS, AG

And to our  
funders:  
NIEHS (16 yrs)  
CDC (3 yrs)  
USEPA (4yrs)  
NIMHHD (2 yrs)

DiNEH and  
NBCS Research  
is reviewed and  
monitored by  
Navajo Nation  
Human  
Research  
Review Board

# Community Health Concerns: 2000

3



- Diabetes: 3-5x >> us as a whole
- CKD: 2.5x; ESRD: 3x;
- early onset: teens on dialysis
- >30% Navajo population lacks access to regulated water – use unregulated wells
- Anthropogenic and natural uranium surface exposures sources

# DiNEH Iterative Assessment

Capacity Building – Multi-directional study design

Surveys



Medical Record Reviews



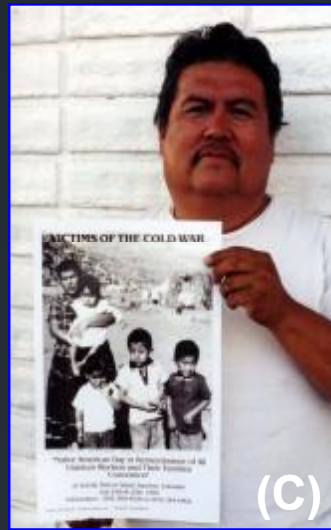
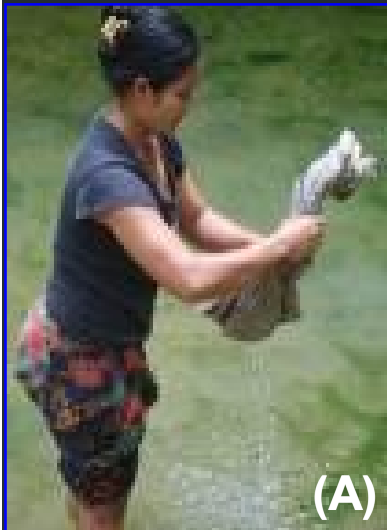
Clinical Assessments



Biomarker Analyses

## DINER Project Results: Active-mining era exposures (workers and family) increased risk of kidney disease

5



Active-mining related exposures were estimated from self-reported survey data

- A: Washed the clothes of a uranium worker (22%)
- B: Worked in a uranium mine (10%)
- C: Lived in a mining camp (4%)
- D: Worked in a uranium mill (2%)
- E: Worked on a uranium mine or mill reclamation or hauled uranium ore or tailings in a pickup truck (2%)

*Many workers have already died from lung cancer, cohort had more family members than workers*

# DiNEH Results: Ongoing environmental legacy exposures → increased risk for hypertension, autoimmune disease, immune dysfunction

6



Exposures estimated from two sources of data:

- 1) The proximity of each resident's home\* to all of the abandoned uranium mine and mill waste features (100)
- 2) Reported activities that may result in exposure to uranium mine and mill wastes

- A: Used materials from abandoned uranium mine or mill (17%)  
B: Herded livestock next to uranium mine, mill or waste dump (13%)  
C: Drunk or contacted uranium mine waste water (13%)  
D: Played on a uranium tailings pile or waste dump (13%)  
E: Played outdoors near a uranium mine, mill, or waste dump (12%)  
F: Sheltered livestock in an abandoned uranium mine (2%)

*\*Note: Median length of residence in current homes was 33 years*



## DiNEH work with NAIHS CUE-JTH

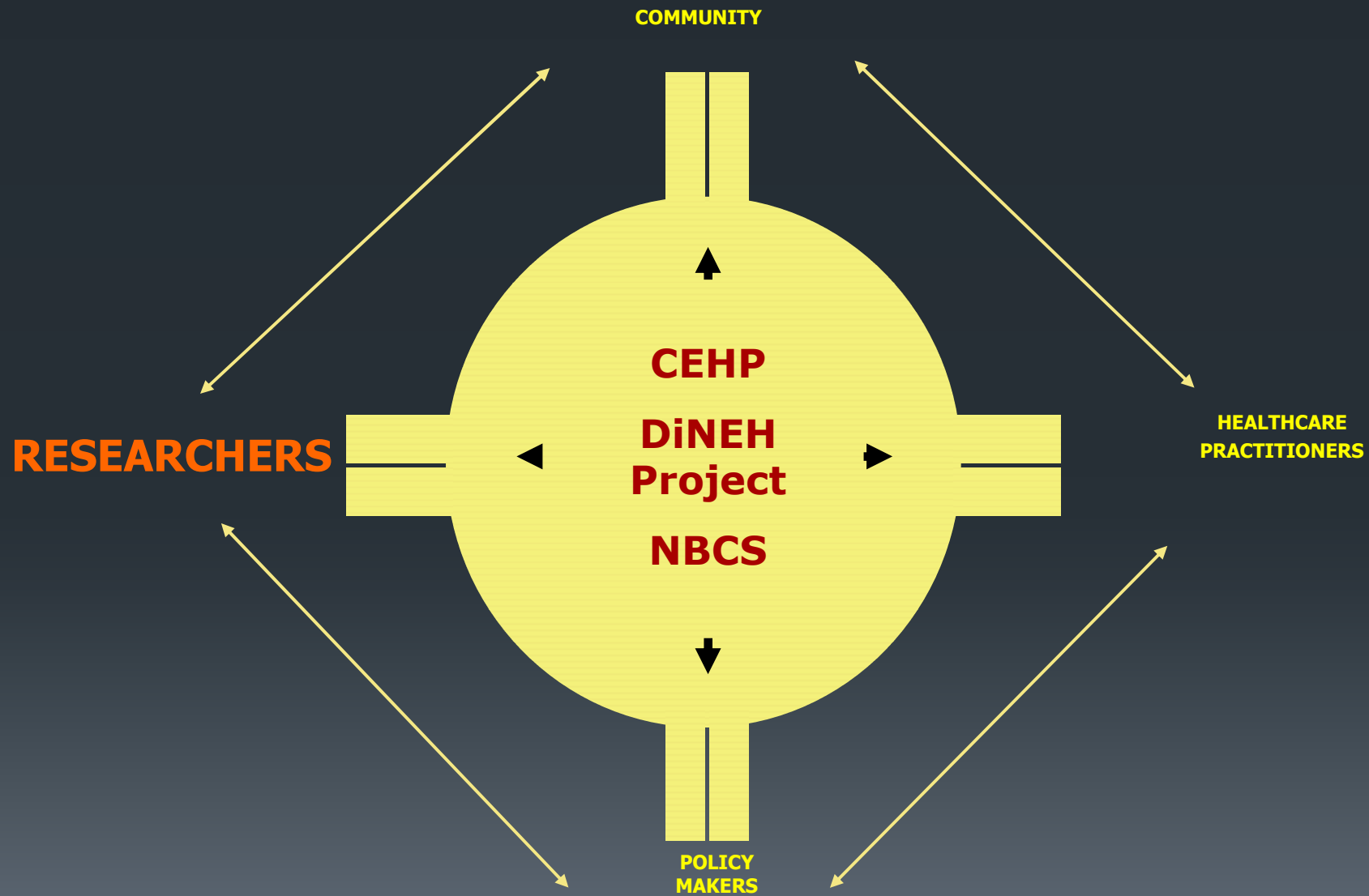


About 90 community members participated in a DiNEH-CUEJTH screening and collection day at Baca Chapter in August 2011.



- Design of long-term surveillance
- Assessments began July 2010; 270 DiNEH participants through 2011
- Standard clinical assessments by CUE-JTH
  - UNM Biomarker analyses for kidney function, immune function, cardiovascular damage
- Validation of survey self-report
- CUE-JTH continuing across Navajo Nation – now >900

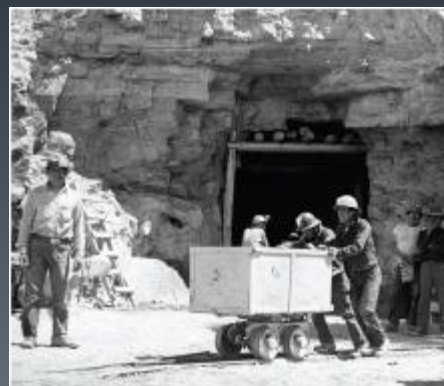
# Mechanisms of Toxicity



# Goal of DiNEH Phase II



- Direct response to community members' requests for research on mechanisms underlying health effects.
- Find early indicators of exposure-related health effects
- Understand mechanisms to develop intervention, prevention

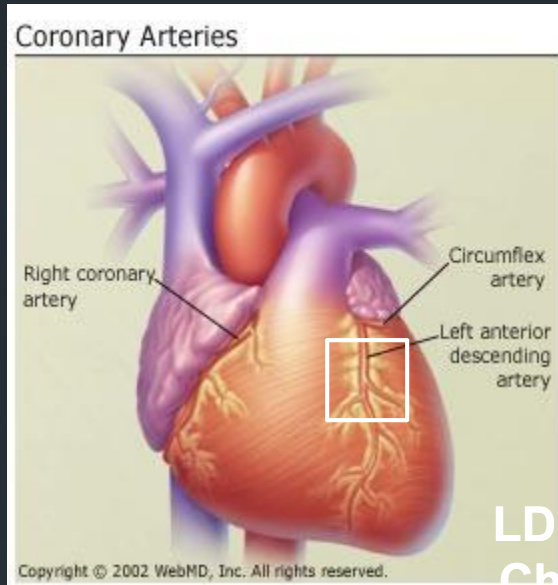


# What do uranium mines have to do with Cardiovascular Disease (CVD) and Diabetes?

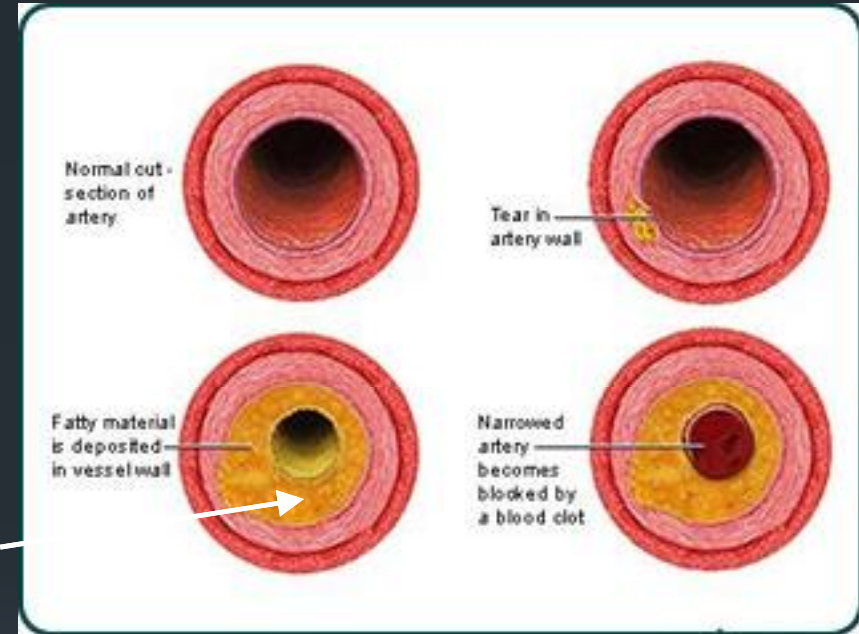


- CVD
  - Prevalence increasing in Navajo community
  - May be promoted or worsened by environmental exposure to heavy metal contaminants
- Diabetes
  - Diabetes also a risk factor for CVD
  - Prevalence increasing in Navajo community
  - Does diabetes increase susceptibility to metals?
    - mine wastes are mixtures of many metals

# Cardiovascular Disease: Atherosclerosis

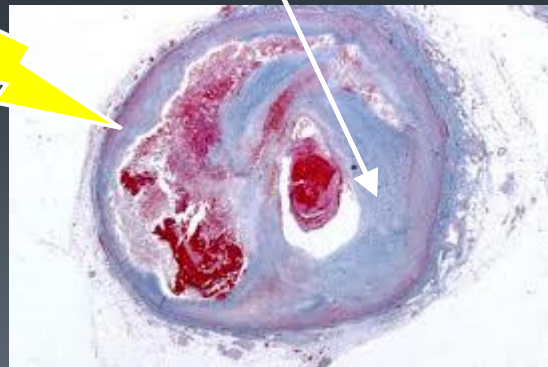


LDL ("Bad")  
Cholesterol



**Metals**

oxLDL  
marker for CVD



Vessel Dysfunction  
Inflammation  
Immune Responses  
Oxidative Stress

# Population Data

Health Condition (self report)	Prevalence in U.S. %	Navajo Cohort (n = 252) %
Type 2 Diabetes	11.3	26.2
Hypertension	25.0	38.1
Heart Disease	11.8	6.0
Stroke	2.7	5.2

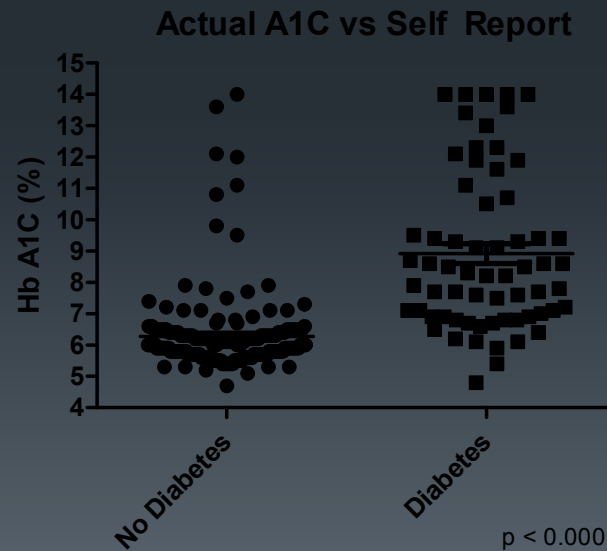
Navajo Cohort: BMI	
New Mexico Average	25.1
Navajo Cohort	30.4

Body Mass Index (BMI)	
Underweight	< 18.5
	18.5—
Normal	24.9
	25.0—
Overweight	29.9
Obese	> 30.0

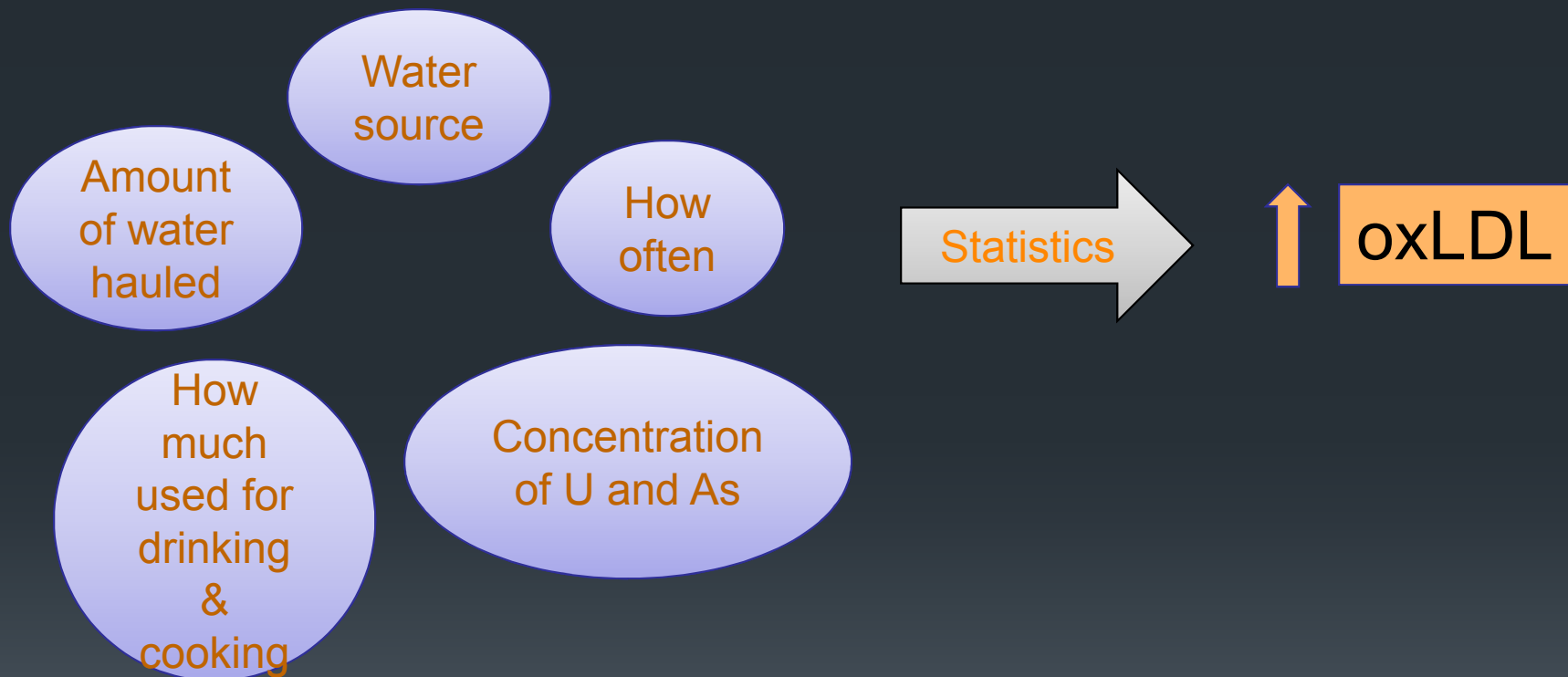
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[http://www.cdc.gov/healthyweight/assessing/bmi/adult\\_bmi/index.html](http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html)

# Population Data

Self-Reported Presence/Absence of Diabetes		A1C Classification	
Navajo Cohort: A1C		Healthy	<5.7%
No Diabetes	6.3%	Pre-Diabetes	5.7-6.4%
Diabetes	8.9%	Diabetes	>6.5%



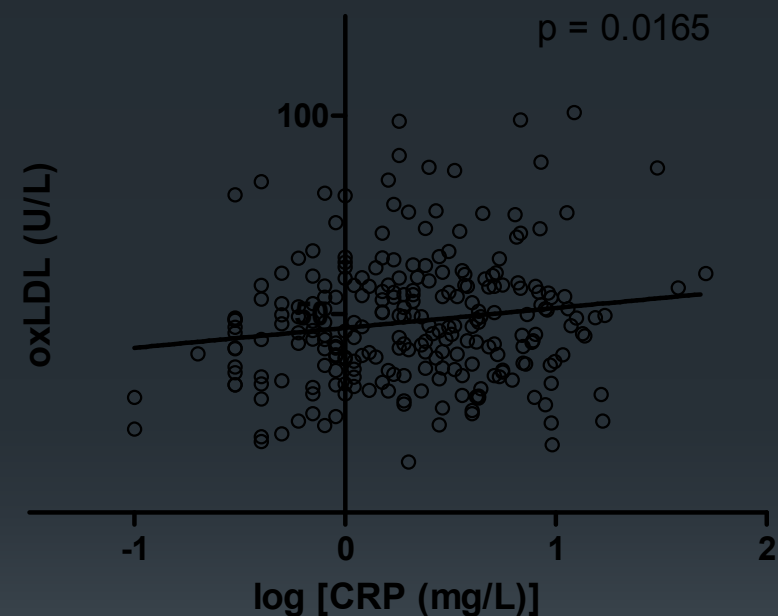
# Water as an exposure source for uranium and arsenic



Total consumption of arsenic and uranium was estimated from several factors

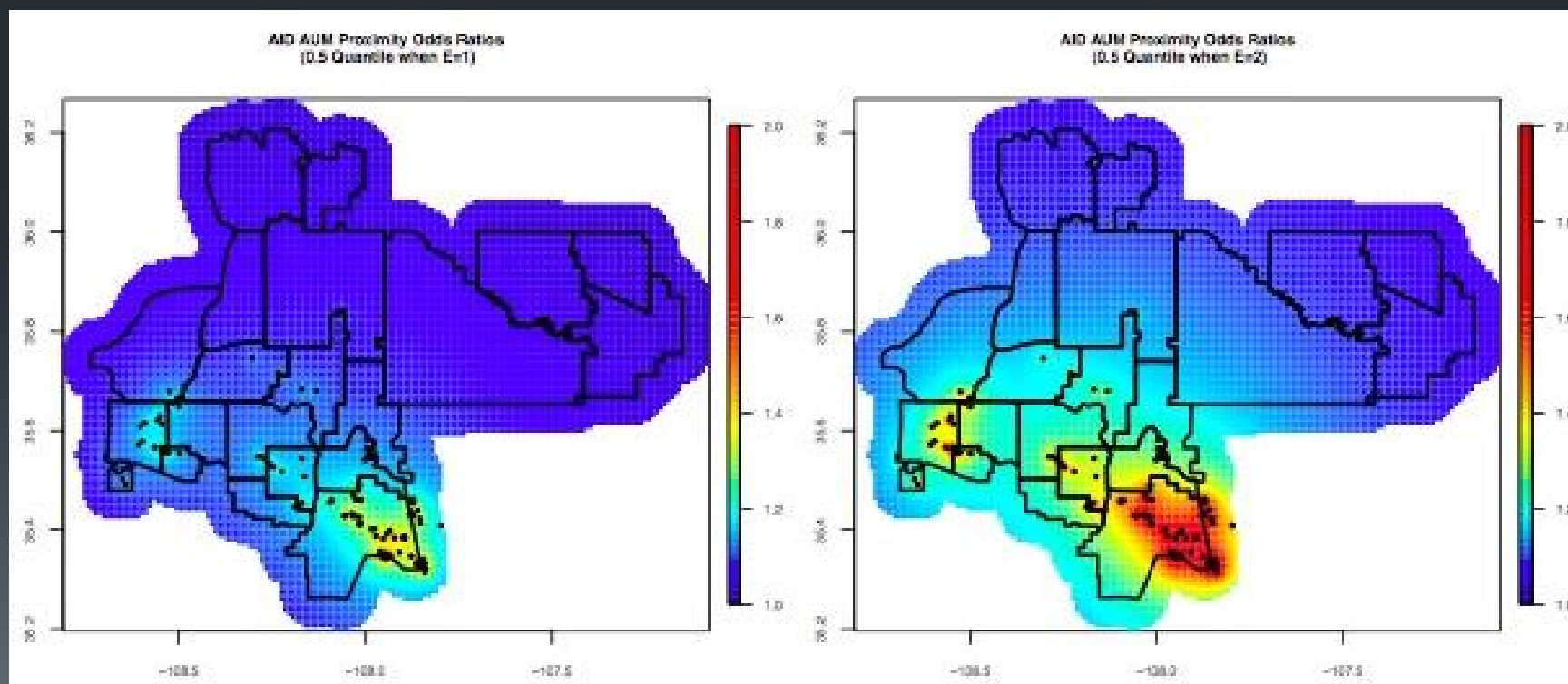
# Inflammation & oxLDL

- C-Reactive Protein (CRP) increases in response to inflammation
- Inflammation is common in CVD and diabetes
- CRP level is a risk factor for atherosclerosis



# Environmental Legacy Exposures Also Increase the Likelihood *Autoimmune Disease*

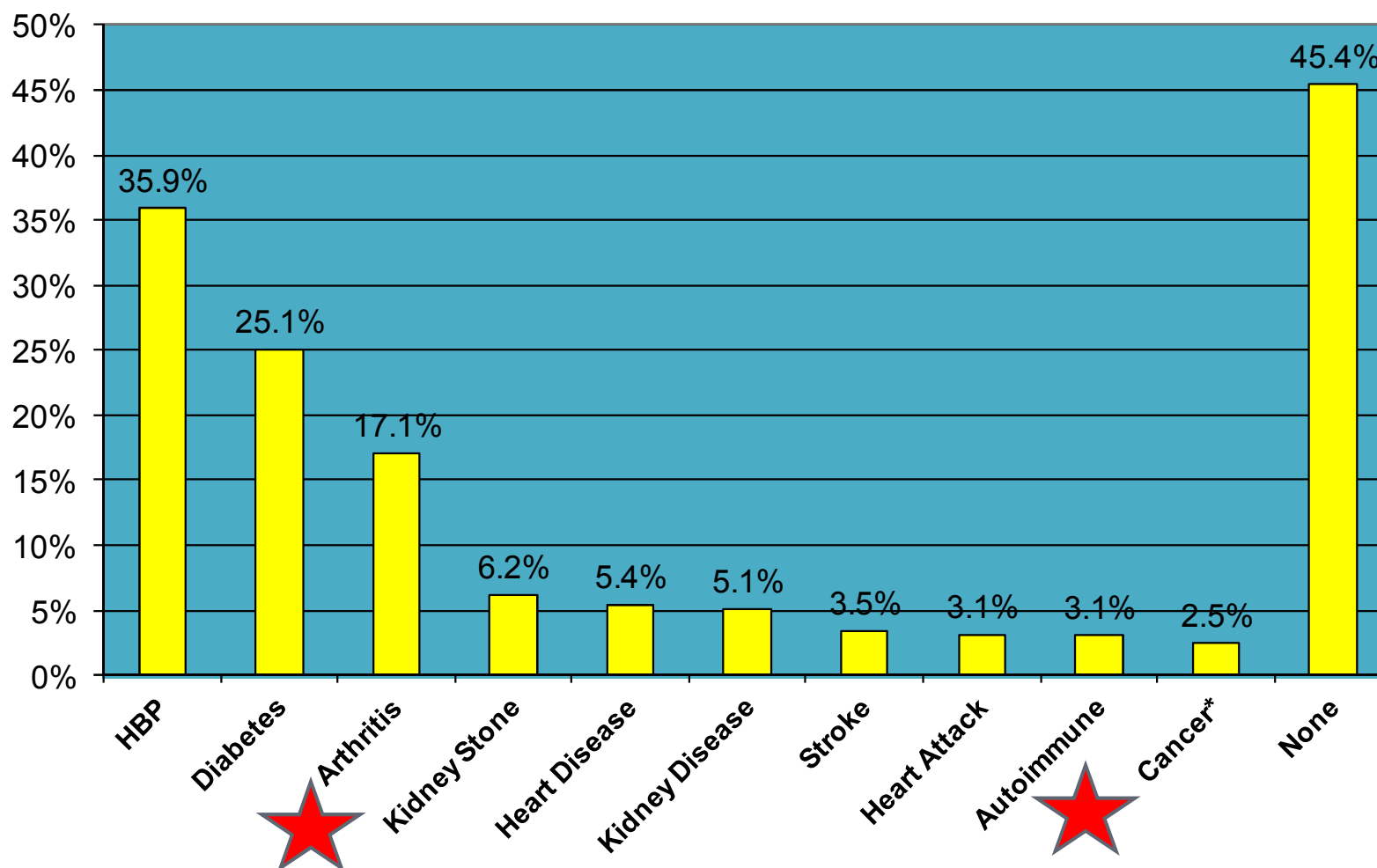
Figures below show increases in risks for *autoimmune disease* (self-reported) based on an increase from 1 to 2 types of exposure activities



# DiNEH Survey Responses

## Prevalence of Self-Reported Health Conditions Among 1,304 DiNEH Survey Participants

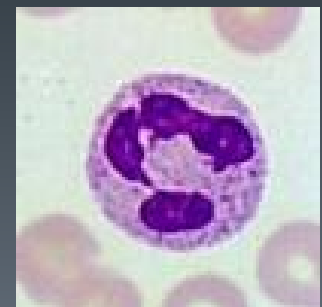
(\*Cancer prevalence based on 1,011 participants surveyed)



# DiNEH biological sample collection

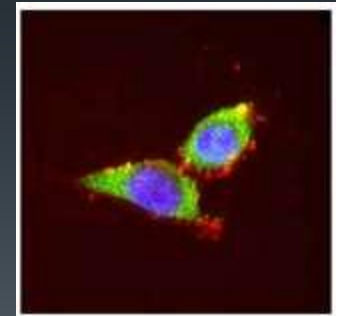
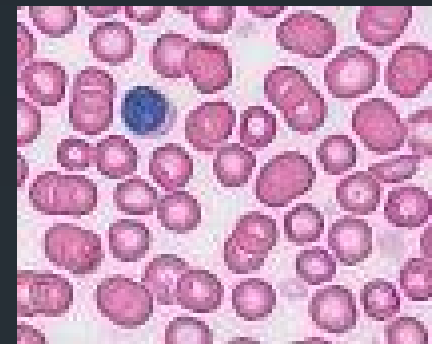


- DiNEH project participants from 20 chapters
- Blood and urine samples were collected from 267 individuals
- A subset has been analyzed for immune biomarkers (N=69)



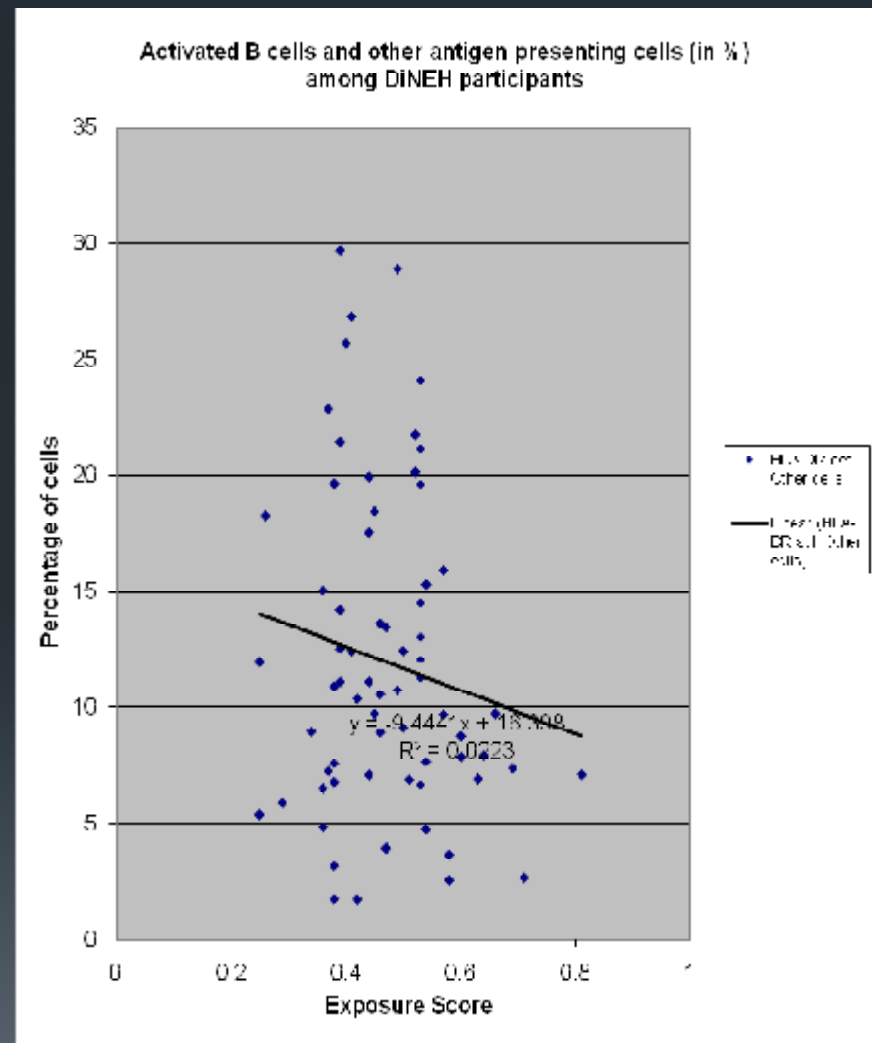
# Flow cytometry measurements (n=69)

- Lymphocyte subpopulations from whole blood samples..
- 6 cell populations were measured:
  - T cells (CD3+), T helpers (CD4+), T suppressors (CD8+);
  - B cells (CD19+);
  - HLA-DR+ cell activation in T cells and
  - B cells and other cell types; NK cells (CD3-/CD16+/CD56+).



# Flow cytometry results II.

- Increased percentage of activated T cells
- Decreased percentage of activated B cells
- Decoupling of T cell and B cell activities suggest altered immune response among this subset of participants
- Can lead to lower production of protective antibodies



# Serum cytokine measurements



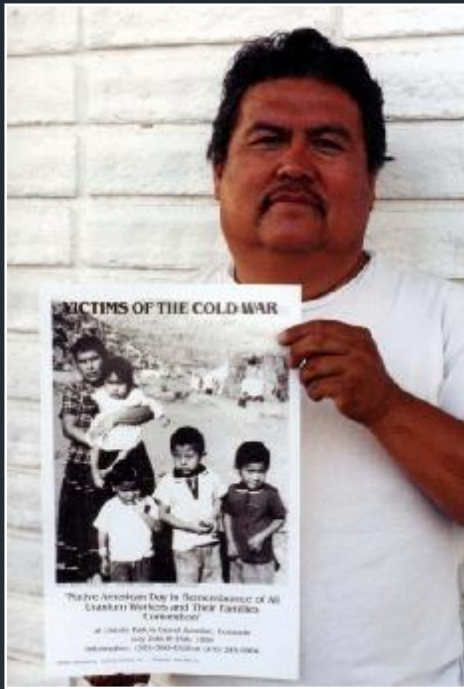
- Detection of 10 human serum cytokines (IL-1 $\beta$ , IL-2, IL-6, IL-8, IL-10, INF- $\gamma$ , TNF- $\alpha$ , and GM-CSF) high sensitivity assay
- Uses only 50  $\mu$ l of serum sample/participant
- Complex task: cytokine production indicative of the presence of an inflammatory response
- Work in progress
- Metal-induced chronic inflammation could be common pathway to both immune and cardiovascular results

# Results of autoantibody production



(IHS LabCorp)

- ANA positivity was 52%, higher than national average (13%)
- Techniques used to detect ANA differ widely between labs
- ANA positivity is known to increase with age
- High titer indicates that connective tissue disease is likely if clinical findings are present.
- False-positive results occur in normal blood donors and in patients with chronic liver disease, neoplasms, or active chronic infections.
- Positive ANA, at least 1 positive disease specific Ab result was also obtained.



Community  
Concerns



Toward a mechanism-  
based intervention

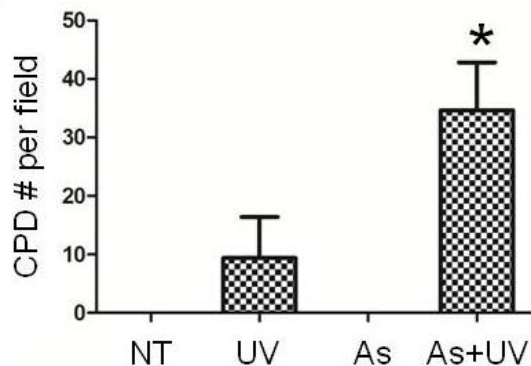


Bench  
Research

# Arsenic increases DNA damage



- Radiation also damages DNA
- If DNA damaged →
  - Repaired, or
  - Reproduce damaged cells, or
  - If germ cell (sperm or egg), pass damage on to next generation



DNA damage (CPDs)

Karen Cooper  
Brenne King

# Arsenic inhibits DNA repair enzyme – also in immune cells



- Inhibits by knocking out zinc – (good metal)
- Lab studies indicate uranium acts in similar way
- Zinc in prenatal vitamins potentially sufficient to reverse
- Uranium + arsenic? Studies in progress

**Navajo Birth Cohort Study  
2010 - present  
Cooperating Organizations**



**Centers for Disease Control and  
Prevention/Agency for Toxic  
Substances and Disease Registry**

**DiNEH Project Team**

- UNM Community Environmental Health Program (CEHP)
- UNM Pediatrics Department, Center for Development and Disability
- Southwest Research and Information Center (SRIC)
- Consultants

**Birth Cohort**

**Navajo mothers,  
fathers and  
babies; other  
community  
members;  
chapters**

**Navajo Area Indian  
Health Service (NAIHS)**

**Navajo Nation  
Division of Health**

**With Help From**

**Growing in Beauty  
(developmental  
disabilities services  
provider)**

**PL93-638 Facilities  
(Tséhootsooí, Tuba City)**

**Other Navajo Nation Agencies  
(Environmental Protection Agency,  
WIC, Health Education,  
Office of Uranium Workers)**

**USEPA  
Region 9**

# NBCS Status

- Funded 2010
- 2.5 years to complete regulatory process
  - 4 IRBs (complete by August 2011)
  - OMB – delayed initial response by several months
    - Final approval not until mid-February 2013
- Recruitment began one-week later: Chinle
- Today, enrollment at Tsehootsooi, Tuba (Kayenta)
- Shiprock scheduled first week of May
- Gallup, Kayenta to follow
- Renewal in progress – May 13

# Outcomes Model Structure

## EXPOSURE INPUTS

### Uranium

Proximity, dust, occupation, water, land use

Survey, GPS, NURE data, Biomonitoring, Existing water quality, in-home dust, parent biomarker analyses

### Radiation

Home scans

Biomonitoring, Existing data

### Radon

In-home

Canister monitoring

## MODIFIERS

### Reproductive History

Mother and father

Survey & Medical Records

### Nutritional Status

Mother

WIC, FFQ, Biomonitoring

### Demographic Variables

Parental income, education, parental ages

Survey

### Alcohol, Substance Abuse

Surveys, Meconium, Medical Record

### Co-Exposures

Other metals, PAHs, Particulates, Sulfur Compounds

Biomonitoring, Surveys, Home Assessments

## REPRODUCTIVE OUTCOMES

### Reproductive Difficulty

Miscarriage, delivery complications

Medical Record

### Low Birth Weight

Medical Record Review

### Congenital Malformation

Medical Record, Survey

## DEVELOPMENTAL OUTCOMES

### Development: Behavior

communication, gross & fine motor skills, problem solving and personal social skills

ASQ-I & Mullen

### Development: Physical

Length, weight, head circumference

Anthropometry

### Development: Medical Infections, Morbidity, Mortality

Medical Record Review

### Development: Biomarker

Inflammation, Immune system

Laboratory Analysis

# NBCS Participant Exposure Assessment

29

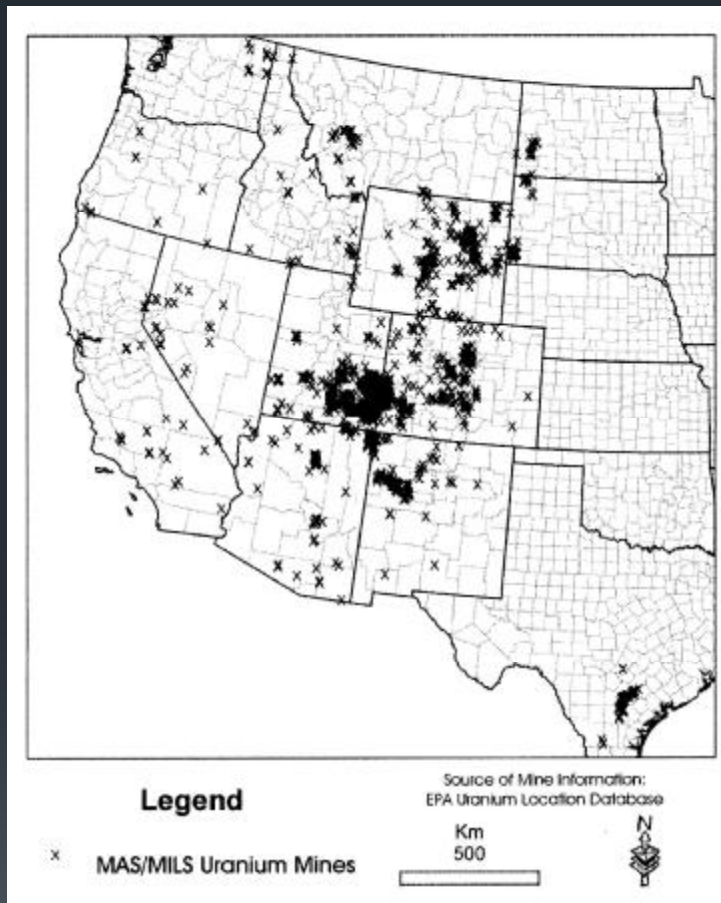
Exposure Source	Methods/Media/Locations	Data Source(s)/Laboratory
<b>Environmental Monitoring – Existing Data + New Sampling</b>		
Ambient air quality	Regional air monitoring stations	USEPA, NNEPA data
Gamma radiation	Screening surveys of indoor, outdoor environments at participant's home using Ludlum-19 or equivalent meter (based on NNEPA SOPs)	De novo screenings with NBCS data sharing; existing data for homes previously screened by NNEPA-SF or USEPA
Indoor dust	Wipe or vacuum samples collected during in-home assessment	USEPA-9 laboratory
Indoor H <sub>2</sub> S	Homes in oil & gas production areas and non-O&G areas (controls)	Hydrogen sulfide tape meters furnished by USEPA, ATSDR
Indoor radon	6-day canisters or E-PERMs placed in home in winter months	USEPA or private company for canisters; NNEPA-Air for electret reading; existing NNEPA data
Proximity to AUMs	Existing electronic dataset of AUM locations, surface areas	USEPA/USACE atlases (w/ metafiles in DVDs)
Water (regulated, unregulated)	Survey responses for water use, water sources	USEPA, NNEPA existing water quality data for previously tested sources; new testing
<b>Personal Historical Exposures – Survey self report</b>		
Historic & current activity patterns of participants contacting wastes, contaminants	Survey questions on land use, water use	Intake surveys of mother, father (NBCS)
Occupations, work-related	Survey questions on work history	Intake surveys of mother, father (NBCS)
<b>Confirmation Biomonitoring – Measurement of toxic materials in biological samples</b>		
Metals, metalloids	Blood and urine samples	CDC Environmental Health Lab; UNM Earth & Planetary Sciences ICP-MS
Alcohol metabolites	Meconium	Contract laboratory or Emory U.
Uranium decay chain isotopes	Meconium	UNM nuclear chemistry laboratory
Polycyclic Aromatic Hydrocarbons	Blood and urine samples	CDC Laboratories

29

# Future of Partnership: Navajo Birth Cohort Study (NBCS)

- Opportunity to confirm DiNEH results in younger population
  - *DiNEH cohort mean age ~55*
  - *NBCS – parents 14-45*
  - *Infants*
- Build research capacity on Navajo
- Model for translation of results
  - Integration with health care
  - Inform policy and regulations
- Incorporate outcomes from DiNEH – continue linkage to mechanistic studies → intervention

# Legacy of Mining in the West



- More than 500,000 abandoned hardrock (excluding coal) mine features in US (Mineral Policy Center) (200,000 mines – EPA)
- Clean-up costs? \$22 mil/site (USEPA, 2001)
- USEPA estimates:
  - ~10,400 abandoned uranium “mine features” in 15 western states
- U.S. Bureau of Mines estimates:
  - ~4,100 discrete uranium mines
  - Source:  
<http://www.epa.gov/rpdweb00/tenorm/uranium.html>
- *Many impact tribal lands (Laguna, Sioux – but also other rural communities (Bluewater Valley)*
- *Wastes are mixtures – synergy?*

## *Oversight, Review and Approval*

- *All research presented here is reviewed and approved by Navajo Nation Human Research Review Board (NNHRRB) and UNM Human Research Review Committee*

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- ***CDC/ATSDR** U01 TS000135; and*
- *Contracts and in-kind support from **USEPA Region 9**; and **Navajo Nation Environmental Protection Agency (NNEPA)***

Is this OK?????????

